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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/371,648 | 08/10/99 | YANAGIMACHI R | 265036600070 |

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| EXAMINER | |
|---|---|
| PARAS JR, P | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | 12 |

**DATE MAILED:** 09/26/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

FILE

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/371,648 | YANAGIMACHI, RYUZO | |
| | Examiner | Art Unit | |
| | Peter Paras, Jr. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☒ Responsive to communication(s) filed on *14 July 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8, and 10-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, and 10-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Applicants' Amendment filed July 14, 2000 (Paper No. 10) has been entered. Claim 9 has been cancelled. Claims 1-3, 10-12, 16, and 21 have been amended. Claims 1-8, and 10-21 are pending and are under current examination.

Prior rejections of record not made of record in the instant Office action have been withdrawn in view of Applicants' arguments and amendments to the claims.

New grounds of rejection: the addition of claims 2-3 in the prior 103 rejection.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 10-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lavitrano et al taken with Kuretake et al.

Claims 2-3 are directed to a method of obtaining a transgenic embryo comprising microinserting a complex of a demembranated or membrane-disrupted sperm head and an exogenous nucleic acid into an unfertilized oocyte to form a transgenic fertilized oocyte and allowing the transgenic fertilized oocyte to develop into a transgenic embryo wherein the microinserting step is accomplished by piezo-electrically actuated microinjection.

Lavitrano et al disclose a method of creating a transgenic mouse comprising incubating live, intact mouse sperm with plasmid DNA (page 718, lines 1-3), fertilizing mouse oocytes with the sperm-DNA complex, transferring the resulting embryos to foster mothers (page 718 column 2 paragraph 1 lines 1-8), and analyzing the offspring by Southern blot of tail DNA for the presence of the transgene (paragraph 2 lines 1-3). Germline transmission of the transgene was established (page 720 column paragraph 1 lines 1-4 and figure 7 page 721). Lavitrano et al disclose that mouse spermatozoa can capture foreign DNA and suggest that DNA can be transferred into egg cell at fertilization (page 721 Discussion lines 1-5).

Lavitrano et al do not expressly disclose the following method step for creating a transgenic mouse: microinjecting a complex of DNA and membrane disrupted or demembranated sperm heads into unfertilized mouse oocytes, in particular Lavitrano et al do not teach the use of a piezo electrically actuated microinjection apparatus to microinject a complex of DNA and membrane disrupted or demembranated sperm heads into unfertilized mouse oocytes.

However, at the time the claimed invention was made, Kuretake et al disclose a method of in vitro fertilization of mouse oocytes comprising microinjecting membrane disrupted or demembranated sperm heads into mouse oocytes (page 790 column 2 paragraphs 2-3). Kuretake et al disclose that live sperm can be either sonicated with triton x-100 to separate the head (page 789 bridging 799 paragraphs 1-2) from the tail. Kuretake further disclose that "damage to the sperm plasma membrane increases the fertilization rate by ICSI

simultaneously fertilizing the same unfertilized oocyte as is consistent with the art of record. Since it has been established that both "live" and "dead" sperm are functionally equivalent and that transgenesis must occur at fertilization when using sperm as vectors for DNA transfer, then it is clear that a means of **increasing the rate of fertilization would also increase the rate of transgenesis**. The basis for preferential use of sperm having a damaged plasma membrane (or dead sperm as defined by the specification, see above) has been provided by Kuretake et al who disclose that sperm with a damaged plasma membrane increase the fertilization rate by ICSI (page 789, paragraph 2, lines 5-6). Additionally, Applicants' use the argument that the success of transgenesis via live sperm DNA transfer correlates to successful transgenesis by a method which relies upon membrane-disrupted or demembranated sperm heads for DNA transfer (see amendment page 5, lines 14-17) and rely on references (on page 4 of the amendment) for support that discuss methods of DNA transfer using live or intact sperm.

Accordingly, it is maintained, in view of the teachings of Kuretake et al, it would have been obvious at the time the claimed invention was made for one of ordinary skill in the art to modify the transgenic mouse method of Lavitrano et al by microinjecting demembranated or membrane disrupted sperm heads complexed with DNA into mouse oocytes, particularly by piezo electrically actuated microinjection. One would have been motivated to do this because Kuretake et al disclose that sperm with a damaged plasma membrane increase the fertilization rate by ICSI (page 789 paragraph 2 lines 5-6) and particularly

since an increase in fertilization rate would also increase the percentage of transgenic mice obtained.

**Conclusion**

**No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Peter Paras, Jr.

Art Unit 1632

Patent Examiner
AU 1632